American Journal of Hematology 64:120–123 (2000)

5q- Syndrome Presenting Chronic Myeloproliferative Disorders-Like Manifestation: A Case Report

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A 28-year-old Japanese woman with suspected essential thrombocythemia (ET) had marked thrombocytosis, mild leukocytosis with normal neutrophil alkaline phosphatase activity, and no anemia. She was monitored without being given any medication. Eleven years later, complete blood counts showed no remarkable changes but some nonlobulated mononuclear megakaryocytes were found in the bone marrow. Cytogenetic analysis revealed deletion of the long arm of chromosome 5 (5q-). Subsequently, hemoglobin and platelet counts decreased gradually, splenomegaly appeared and progressed, after which myelofibrosis developed. Acute leukemia developed 16 years after the first documentation of thrombocytosis. 5q- syndrome is known to be a myelodysplastic syndrome (MDS) with unique clinical features and cases with this syndrome presenting with thrombocytosis of more than 1,000 × 10^9/L but without anemia are rare. Furthermore, it is noteworthy that in this patient transition to acute leukemia occurred following development of myelofibrosis and marked splenomegaly, which are generally observed in blastic crises resulting from chronic myeloproliferative disorders (CMPD). The patient showed features indicative of CMPD rather than of MDS in spite of presenting with 5q- chromosomal abnormality. This case supports the concept of "mixed myelodysplastic and myeloproliferative syndromes" and suggests the possibility of the appearance of CMPD-like manifestations in 5q- syndrome. Am. J. Hematol. 64:120–123, 2000.

Key words: 5q- syndrome; myelodysplastic syndrome; myeloproliferative disorders

INTRODUCTION

Myelodysplastic syndromes (MDS) and chronic myeloproliferative disorders (CMPD) are clonal stem cell disorders [1,2]. Typical cases with MDS, except for cases of chronic myelomonocytic leukemia (CMML), show normocellular or hypercellular bone marrow, dysplastic changes in hematopoietic cells, and cytopenia in the peripheral blood [3]. In CMPD patients, a marked increase in the number of mature and immature cells in the blood and bone marrow occurs, but there are no rigid criteria for dysplastic changes. In addition, some cases present mixed features of MDS and CMPD [4].

5q- syndrome has been described as a unique hematological disorder characterized by the following features: interstitial deletion of the long arm of chromosome 5 (5q-), macrocytic anemia, female predominance, normal or high platelet counts, bone marrow erythroid hypoplasia, megakaryocytic hypolobulation, bone marrow blast counts of less than 20%, and relative favorable prognosis [5–7]. At present, 5q- syndrome has been assigned to a subtype of primary MDS FAB-type refractory anemia (RA) with the sole karyotypic abnormality being 5q- [8].

We previously reported a female case with 5q- syndrome presenting essential thrombocythemia (ET)-like findings [9]. Later she suffered from myelofibrosis and huge splenomegaly, followed by an acute blastic crisis with 5q-. She presented a CMPD-like profile during her

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Received for publication 18 March 1999; Accepted 5 January 2000

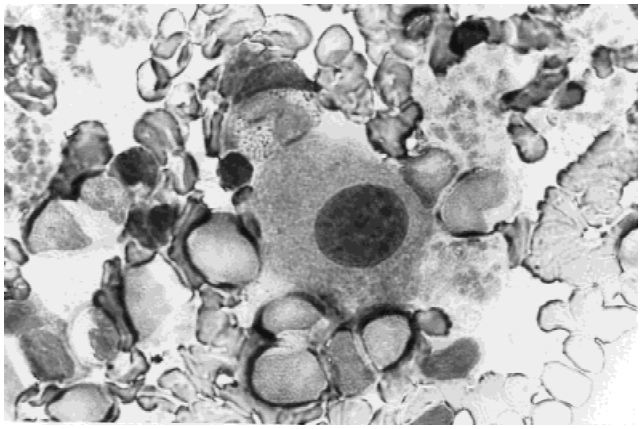

Fig. 1. Bone marrow aspiration smear (May–Grünwald–Giemsa staining) on November 1992 showing a round and nonlobulated megakaryocyte (×400). It is much larger than other mononuclear cells and is visible as if it is about to release platelets.

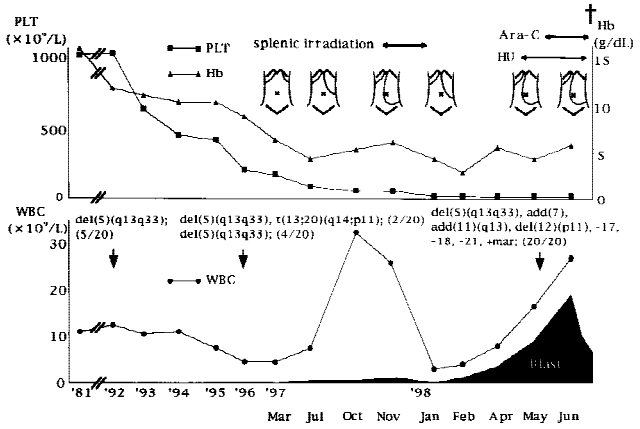

Fig. 2. Clinical course of the patient. HU, hydroxyurea; Ara-C, cytarabine.

disease history, leading us to propose a 5q- syndrome subgroup, which should be assigned to CMPD, not to MDS.

CASE REPORT

A 28-year-old Japanese woman visited a hospital, complaining of upper abdominal discomfort in March 1981. No abnormalities were noted at the physical examination, but thrombocytosis was detected. The peripheral complete blood count (CBC) was as follows: hemoglobin (Hb), 15.9 g/dL; MCV, 89.2 fL; white blood cells (WBC), 11 × 10^9/L with differentials of 8% bands, 57% segments, 1% basophils, 3% eosinophils, 8% monocytes, 23% lymphocytes; and platelets, 1,060 × 10^9/L. Bone marrow aspiration revealed normal morphology. Although no chromosomal analysis was performed, normal activity of neutrophil alkaline phosphatase ruled out chronic myelogenous leukemia. She was suspected of having CMPD, specifically ET, but she had no subjective symptoms and was therefore followed up without receiving any medication. CBCs revealed no remarkable changes from the first visit until May 1984, at which time the follow-up was stopped. She visited our hospital on September 8, 1992 with erythromelalgia of the upper extremities, which disappeared after the administration of aspirin. The CBC on November 17, 1992 was as follows: Hb, 11.9 g/dL; MCV, 95.4 fL; WBC, 10.1 × 10^9/L with differentials of 2% bands, 64% segments, 3% basophils, 3% eosinophils, 4% monocytes, 24% lymphocytes; and platelets, 1,050 × 10^9/L.

Bone marrow aspiration revealed some non-lobulated mononuclear megakaryocytes (Fig. 1) with normal morphology in the erythroid and myeloid series. Ringed sideroblasts could not be detected with iron staining. Cytogenetic analysis revealed a deletion between 5q13 and 5q33 (del(5)(q13q33)) in five of 20 metaphases. Her Hb level and platelets count gradually decreased. In September 1996, CBC revealed anemia and normalization of platelets count: Hb, 8.5 g/dL; MCV, 98.1 fL; WBC, 4.2 × 10^9/L with differentials of 5% bands, 57% segments, 3% basophils, 7% eosinophils, 4% monocytes, 24% lymphocytes; and platelets, 225 × 10^9/L. Bone marrow findings were similar to those obtained in 1992. Cytogenetic analysis revealed del(5)(q13q33) in four, and del(5)(q13q33), t(13;20)(q14;p11) in two of 20 metaphases. In March 1997, splenomegaly was first detected. Splenomegaly, anemia, and thrombocytopenia rapidly progressed, and blastic cells were detected in the peripheral blood (Fig. 2). The patient needed blood transfusions and had lost 7 kg of body weight during the preceding year. She was admitted on November 11, 1997.

On admission, she complained of malaise and abdominal fullness. She had a low-grade fever and was emaciated. Severe anemia and enlargement of the spleen, with the edge descending 5 cm below the navel, were noted. CBC revealed: Hb, 6.3 g/dL; MCV, 92.2 fL; WBC, 26.5 × 10^9/L with differentials of 2% blasts, 1.5% promyelocytes, 12.5% myelocytes, 19% metamyelocytes, 26.5% bands, 4.5% segments, 13% basophils, 13.5% eosinophils, 3% monocytes, 4.5% lymphocytes; and platelets, 21 × 10^9/L. Bone marrow aspirate yielded a dry tap while trephine biopsy showed severe myelofibrosis (Fig. 3).

The patient received blood transfusions and low-dose radiation for the huge splenomegaly. Since February 1998, the blasts count in the peripheral blood increased to more than 20% of WBCs (Fig. 2). Cytogenetic study revealed del(5)(q13q33), add(7), add(11)(q13), del(12)(p11), -17, -18, -21, +mar in 20 of 20 metaphases. Hydroxyurea and low dosage of cytarabine were adminis-

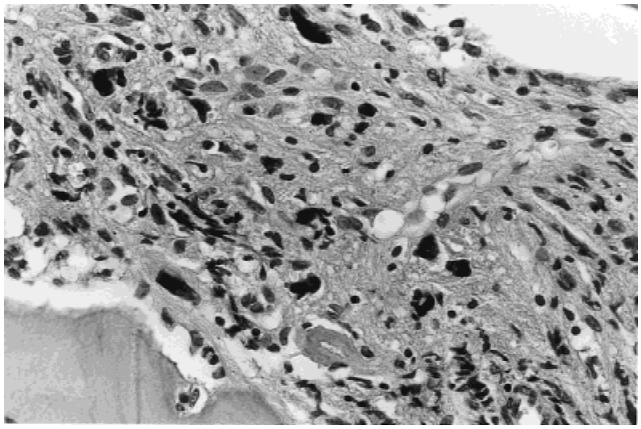

Fig. 3. Specimen of bone marrow biopsy (hematoxylin–eosin staining) on October 1997 showing severe myelofibrosis and proliferation of mononuclear megakaryocytes (×100).

tered but they were not effective. The patient died of intrathoracic infiltration of blasts and intra-abdominal bleeding in July 1998.

DISCUSSION

5q- syndrome has been described as a clinical manifestation of hematological disorders with some unique features [5–7] and has been classified as MDS RA type [8]. Various break points in the 5q chromosome have been reported in 5q- syndrome. In our case, the chromosomal deletion detected was del(5)(q13q33), which is the most common and has the best prognosis [10].

Chromosomal abnormalities, especially 5q-, in ET are suggested to be the result of therapy (^{32}P, alkylating agents, or both)-induced changes [11,12]. Although Reis [13] reported a case of ET with a single 5q- abnormality and without any history of prior chemotherapy, this case did not have the morphological features associated with 5q- syndrome, including erythroid hypoplasia and hypolobulated megakaryocytes. Eleven years from the first documentation of thrombocytosis, the platelets count of our patient was still over $1{,}000 \times 10^9$/L, and a single 5q- chromosomal abnormality accompanied by increasing levels of hypolobulated megakaryocytes in the bone marrow, which are characteristics of 5q- syndrome, was detected during this period. Her clinical status was a mixture of ET and 5q- syndrome characteristics. Kerkhofs reported that one of 34 hematological disorder patients with 5q- showed similar findings to those of our case [14]. Such cases, although apparently rare, suggest the existence of a subgroup of 5q- syndrome with proliferative characteristics.

Furthermore, it is noteworthy that our case transformed into acute leukemia following development of myelofibrosis and huge splenomegaly, which are generally observed in blastic crisis resulting from CMPD. When patients with MDS suffer from myelofibrosis, they usually do not have obvious organomegaly [15]. Pegliuca analyzed 10 cases of MDS with myelofibrosis and concluded that obvious visceromegaly and extramedullary hematopoiesis are absent and trilineage dysplasia is present in MDS with myelofibrosis, and can be used to distinguish MDS from chronic idiopathic myelofibrosis (CIMF) [16]. Nevertheless, according to a report by Verhoef, seven of 22 MDS with myelofibrosis patients had marked splenomegaly and two showed extramedullary hematopoiesis [17]. Reilly [18] described a patient suffering from myelodysplasia and myelofibrosis associated with hepatosplenomegaly and possible extramedullary hematopoiesis as identified by ferrokinetic studies. They proposed the term "transitional myelodysplasia-myelofibrosis" for this condition. Our case demonstrated a clinical profile that might fit such a concept.

MDS has been classified into five subtypes by the FAB co-operative group [19], although there have been reports of MDS cases difficult to assign to any of the FAB subtypes [4,20]. Neuwirtová and colleagues used the term "mixed myelodysplastic and myeloproliferative syndromes (MDS-MPS)" for patients showing myelodysplasia according to the FAB classification and an increase in the number of platelets or leukocytes [21]. As our patient lacked macrocytic anemia and did not show all the morphological features of 5q- syndrome, she might not be classified as a classical 5q- syndrome patient. It is, however, interesting that despite showing the common chromosomal deletion and the typical megakaryocytic morphology of 5q- syndrome, her clinical manifestations were more similar to those of CMPD (first ET, then CIMF followed by blastic transformation) rather than to those of MDS. Our case appears to support the concept of "mixed MDS-MPS" [21] or "transitional myelodysplasia-myelofibrosis" [18], and suggests that some 5q- syndrome patients may display CMPD-, not MDS-, like manifestations.

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